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Re: Docket No. 2004D-0035
Draft Guidance for Industry on the Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis
Request for Comments

Dear Sir or Madam:

Reference is made to the Draft Guidance for Industry on the Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis (April 1994). The FDA requested comments on this guidance because a significant body of data related to the diagnosis, prevention and treatment of osteoporosis had been published. In response to this request, submitted herewith, are comments from GlaxoSmithKline Consumer Healthcare (GSKCH) regarding the draft guidance.

In summary, GSKCH proposes that:

a) clinical trials for osteoporosis drugs require patients to take supplemental calcium and vitamin D
b) the daily level of supplemental calcium and vitamin D should be from 500-2000 mg of calcium and from 250-800 IU of vitamin D.

The rationale for this request is provided below.

We recognize that there are safe and effective therapies for osteoporosis available for patients with bone mineral density scores that indicate low bone mass as well as for patients that have suffered an osteoporosis-related fracture. The approval of these drugs was based upon clinical trials in which all patients (both active and placebo groups) had adequate intakes of calcium and vitamin D. Eastell[(1)] has recently reviewed the literature and documents that the efficacy of the anti-osteoporosis drugs that resulted in the approval by FDA was in large part dependent upon the adequate intake of calcium and vitamin D in conjunction with drug intake. In virtually all of the clinical trials that resulted in anti-osteoporosis drug approval, supplements of calcium and vitamin D were provided to participants in both the "placebo" arm as well as the active arm. The dosages ranged from 500 to 1000 mg/day of elemental calcium and from 250 to 600 IU of vitamin D, usually as vitamin D3[(1)].

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The reason that supplements of calcium and vitamin D were provided to study participants was that most osteoporotic patients were not getting adequate calcium and/or vitamin D in their diets. This has been documented in the US, as well as in other nations where anti-osteoporosis drug trials have been done[2]. Moreover, recent publications document the low intakes of both calcium and vitamin D in patients currently taking anti-osteoporosis drugs post FDA approval[1-3]. The fact is that newer drugs which actually build bone and other drugs in clinical trials that utilize other mechanisms of action may require even higher intakes of calcium and vitamin D to optimize their effects.

At present, the current approved drug label and patient information do not clearly advise patients to take supplements of calcium and vitamin D. Also, the current clinical protocols for investigational drugs do not clearly indicate the requirement for supplemental calcium and vitamin D. Thus, we strongly recommend that FDA request that both the label and patient information instructions for anti-osteoporosis drugs include definitive statements about the need for the use of calcium and vitamin D supplements. We suggest that all new clinical trials that test the safety and efficacy of anti-osteoporotic drugs include clear directions in the protocol that each patient receive a calcium and vitamin D supplement that contains dosages ranging from 500- 2000 mg of elemental calcium and 250 - 800 IU of vitamin D. Likewise, we request that currently marketed anti-osteoporosis drugs strengthen the advice to patients concerning the need for supplemental calcium and vitamin D to help assure drug efficacy.

We appreciate this opportunity to provide comments. Please contact me if you have any questions.

Sincerely,

Anthony Amitrano

Anthony Amitrano
Director,
Regulatory Affairs

Cc: Adrianne Bendich, Ph.D., FACN

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1. Eastell, R. Calcium requirements during treatment of osteoporosis in women. In: Preventive Nutrition: The Comprehensive Guide for Health Professionals, Third Edition, Adrianne Bendich and Richard J. Deckelbaum, eds., Humana Press, Totowa NJ, 2005, pp 425-432.

2. Stafford RS, Drieling RL, Hersh AL. National trends in osteoporosis visits and osteoporosis treatment, 1988-2003. Arch Intern Med. 164:1525-30, 2004.

3. Holick, MF., Siris, ES., Binkley, N., et al., Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinal Metab 90: 3215-3224, 2005.